

Integrating Clinical, Genetic, Genomic, and Molecular Phenotype Data to Dissect a Complex Trait

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Abstract:

Gene mapping has been extremely successful for simple Mendelian diseases; however, finding such genes for diseases, and their associated risk traits, that are of public health interest has proven difficult. Reasons for this difficulty include disease heterogeneity (disease sub-types with some or no overlapping genetic causes), misclassification (from using discrete classifications of disease from thresholds and combinations of thresholds), and cumulative environmental influences. With the advent of technology to measure changes in gene expression, i.e. changes in mRNA transcript abundance, it should be possible to unravel some of the complexity existing for these common diseases by incorporating genetic variation, patterns of genetic inheritance, measures of relevant environmental influences and gene expression components. As an initial step in establishing the power of such a combined approach, we apply statistical genetics approaches to variations in mRNA transcript abundances in segregating populations to uncover the strength of genetic signature in mouse, plant and human populations. We examine obesity in a murine cross to demonstrate the power of analytical methods that combine genetic, gene expression, and clinical data. We identify patterns of expression that define obesity subtypes, and genetic analysis reveals that these subtypes are under the control of different loci. These analyses result in the identification of genes and pathways associated with obesity. Our results highlight the potential clinical applications and other possibilities that exist in employing a more comprehensive genetics and functional genomics approach to the study of complex diseases.